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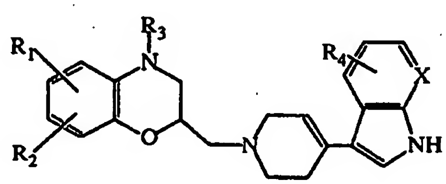

(I)

(57) Abstract

Compounds are provided having formula (I) wherein: R_1 is hydrogen or halogen; R_2 is hydrogen, alkoxy or carboximide; R_3 is hydrogen, alkyl, alkylaryl, aryl or substituted aryl; R_4 is hydrogen, CN, halogen, or carboximide; and X is CH or N; or a pharmaceutically acceptable salt thereof which are useful as anxiolytic and/or antidepressant agents.

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3,4-DIHYDRO-2H-BENZO[1,4]OXAZINE DERIVATIVES

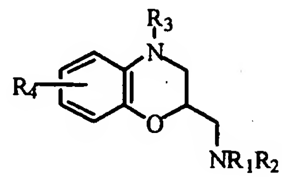
FIELD OF THE INVENTION

This invention is directed to compounds useful in the treatent of neuroloical disease caused by disorders of the serotonin-affected neurological systems. such as depression and anxiety. More specifically, the present invention is directed to 3,4-dihydro-2H-benzo[1,4]oxazine derivatives useful as anxiolytic and/or antidepressant agents.

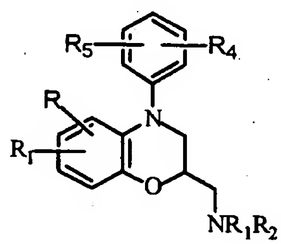
BACKGROUND OF THE INVENTION

Compounds which enhance the neurotransmission of serotonin (5-HT) are known to be useful for the treatment of many psychiatric disorders, including depression and anxiety. The first generation of non-selective serotonin-affecting drugs operated through a variety of physiological means which caused them to possess numerous undesired side effects. The more currently prescribed drugs, the selective serotonin reuptake inhibitors (SSRIs), act predominately by inhibiting 5-HT, which is released at the synapses, from being actively removed from the synaptic cleft via a presynaptic serotonin transport carrier. Since SSRIs require several weeks before they exert their full therapeutic effect, this 5-HT blockade mechanism cannot fully account for their therapeutic activity. It is speculated that this two week induction which occurs before a full antidepressant effect is observed, is due to the involvement of the 5-HT1A autoreceptors which suppress the firing activity of 5-HT neurons, causing a dampening of the therapeutic effect. Studies suggest that after several weeks of SSRI administration, a desensitization of the 5-HT autoreceptors occurs allowing a full antidepressant effect in most patients (see e.g., LePoul et al., Arch. Pharmacol., 352:141 (1995)). Hence, it is believed that overriding this negative feedback by using 5HT1A antagonists would potentially increase and accelerate the clinical antidepressant response. Recent studies by Artigas et al., Trends Neurosci., 19:378-383 (1996) suggest a combination of 5-HT1A activity and inhibition of 5-HT uptake within a single molecular entity can achieve a more robust and fast-acting antidepressant effect.

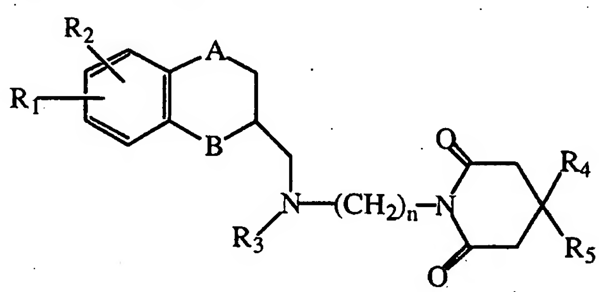
U.S. Patent No. 3,058,980 discloses the preparation of compounds of the following formula which are known to exhibit analgesic activity.



WO 8907596-A discloses the preparation of compounds having the following formula which are active in a variety of CNS disorders, including depression and schizophrenia.



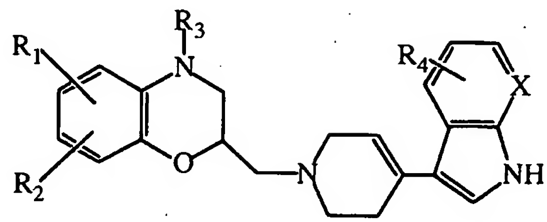
U.S. Patent No. 4,612,312 discloses compounds of the following formula as anxiolytic and antihypertensive agents.



SUMMARY OF THE INVENTION

The present invention relates to a new class of molecules which have the ability to act at the 5-HT1A autoreceptors and concommitantly with the 5-HT transporter. Such compounds are therefore potentially useful for the treatment of depression as well as other serotonin disorders.

The compounds of this invention are 3,4-dihydro-2H-benzo[1,4]oxazine derivatives represented by Formula I:



I

wherein:

R_1 is hydrogen or halogen;

R_2 is hydrogen, alkoxy or carboximide;

R_3 is hydrogen, alkyl, alkylaryl, aryl or substituted aryl;

R_4 is hydrogen, CN, halogen or carboximide; and

X is CH or N; or a

pharmaceutically acceptable salt thereof.

DETAILED DESCRIPTION OF THE INVENTION

Preferably, the compounds of the present invention are those of Formula I, wherein

R_1 is hydrogen; and/or

R_2 is alkoxy or hydrogen; and/or

R_3 is hydrogen, alkyl or alkylaryl; and/or

R_4 is halogen or hydrogen; and/or

X is CH or N; or

a pharmaceutically acceptable salt thereof.

More preferably, the compounds of the present invention are:

2-[4-(5-Fluoro-1H-indol-3-yl)-3,6-dihydro-2H-pyridin-1-ylmethyl]-8-methoxy-3,4-dihydro-2H-benzo[1,4]oxazine;

2-[4-(5-Fluoro-1H-indol-3-yl)-3,6-dihydro-2H-pyridin-1-ylmethyl]-8-methoxy-4-methyl-3,4-dihydro-2H-benzo[1,4]oxazine;

2-[4-(5-Fluoro-1H-indol-3-yl)-3,6-dihydro-2H-pyridin-1-ylmethyl)-8-methoxy-4-ethyl-3,4-dihydro-2H-benzo[1,4]oxazine;

2-[4-(5-Fluoro-1H-indol-3-yl)-3,6-dihydro-2H-pyridin-1-ylmethyl]-8-methoxy-4-propyl-3,4-dihydro-2H-benzo[1,4]oxazine;

2-[4-(1H-Indol-3-yl)-3,6-dihydro-2H-pyridin-1-ylmethyl]-3,4-dihydro-2H-benzo[1,4]oxazine;

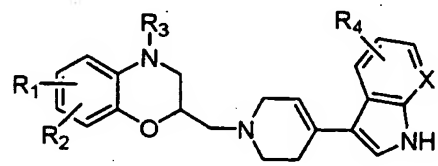
4-Phenyl-2-[4-(1H-pyrrolo[2,3,b]pyridin-3-yl)-3,6-dihydro-2H-pyridin-1-ylmethyl]-3,4-dihydro-2H-benzo[1,4]oxazine; and

2-[4-(5-Fluoro-1H-indol-3-yl)-3,6-dihydro-2H-pyridin-1-ylmethyl]-8-methoxy-4-(4-trifluoromethyl-phenyl)-3,4-dihydro-2H-benzo[1,4]oxazine.

As used herein, the terms "alkyl" and "alkoxy" are meant to include both straight and branched carbon chains containing 1-6 carbon atoms. The term "aryl" is meant to include aromatic radicals of 6-12 carbon atoms. The term "halogen" is meant to include fluorine, chlorine, bromine, and iodine.

The compounds of this Formula I also may be used in the form of a pharmaceutically acceptable acid addition salt having the utility of the free base. Such salts, prepared by methods well known to the art are formed with both inorganic or organic acids, for example: fumaric, maleic, benzoic, ascorbic, pamoic, succinic, bismethylenesalicylic, methanesulfonic, ethanedisulfonic, acetic, oxalic, propionic, tartaric, salicyclic, citric, gluconic, lactic, malic, mandelic, cinnamic, citraconic, aspartic, stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic, benzene-sulfonic, hydrochloric, hydrobromic, sulfuric, cyclohexylsulfamic, phosphoric and nitric acids.

The compounds of the present invention may be prepared by any suitable method which will be recognized by those skilled in the art. Accordingly this invention provides a process for preparing a compound of formula I:



(I)

wherein:

R_1 is hydrogen or halogen;

R_2 is hydrogen, alkoxy or carboximide;

R_3 is hydrogen, alkyl, arylalkyl, aryl or substituted aryl;

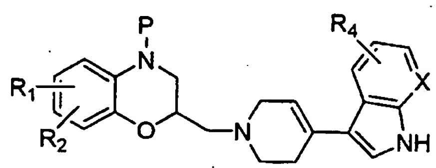
R_4 is hydrogen, CN, halogen or carboximide; and

X is CH or N; or

a pharmaceutically acceptable salt thereof,

which comprises one of the following:

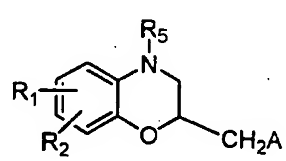
a) deprotecting a compound of formula II



(II)

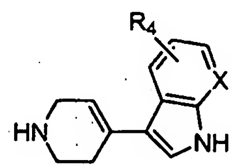
wherein R_1, R_2, R_4 and X are as defined above and P is an amino protecting group to give a compound of formula I wherein R_3 is hydrogen; or

b) reacting a compound of formula III



(III)

wherein R_1 and R_2 are as defined above, A is a leaving group selected from halogen or an organic sulphonyloxy group, e.g. aryl or alkylsulphonyloxy group such as tosyloxy, and R_5 is alkyl, arylalkyl, aryl, substituted aryl or an amino protecting group P as defined above, with a compound of formula IV



(IV)

wherein R_4 and X are as defined above, and if required removing a protecting group P if present, to give a compound of formula I; or

c) acidifying a basic compound of formula I with a pharmaceutically acceptable acid to give a pharmaceutically acceptable salt.

or

d) resolving a mixture (e.g racemate) of optically active isomers of a compound of formula I to isolate one enantiomer or diastereomer substantially free of the other enantiomer or diastereomers

With regard to process a) the removal of a protecting group can be achieved by methods known in the art, e.g. when the protecting group is BOC it can be removed by using trifluoroacetic acid as shown hereinafter in Examples 1 and 5.

Process b) may be carried out under basic conditions, e.g. in the presence of DMSO with heating if required. If R_3 is required to be hydrogen then an amino protecting group, as defined above, should to be present before the reaction is undertaken. This is subsequently removed as detailed in process a) to achieve the desired compound of formula I.

The compounds of formula I may be isolated in the form of a salt of a pharmaceutically acceptable acid, e.g. an organic or inorganic acid by treatment with an acid such as described above.

The compounds of formula I can possess at least one asymmetric centre and accordingly the compounds may exist and be isolated in a number of optically active stereoisomeric forms. This invention encompasses the compounds of formula I in any optically active form or mixtures thereof eg, racemates. Standard separation techniques may be used to isolate particular enantiomeric or diastereomeric forms. For example a racemic mixture may be converted to a mixture of optically active diastereoisomers by reaction with a single enantiomer of a 'resolving agent' (for example by diastereomeric salt formation or formation of a covalent bond). The resulting mixture of optically active diastereoisomers may be separated by standard techniques (e.g crystallisation or chromatography) and individual optically active diastereoisomers then treated to remove the 'resolving agent' thereby releasing the single enantiomer of the compound of the invention. Chiral chromatography (using a chiral support, eluent or ion pairing agent) may also be used to separate enantiomeric mixtures directly.

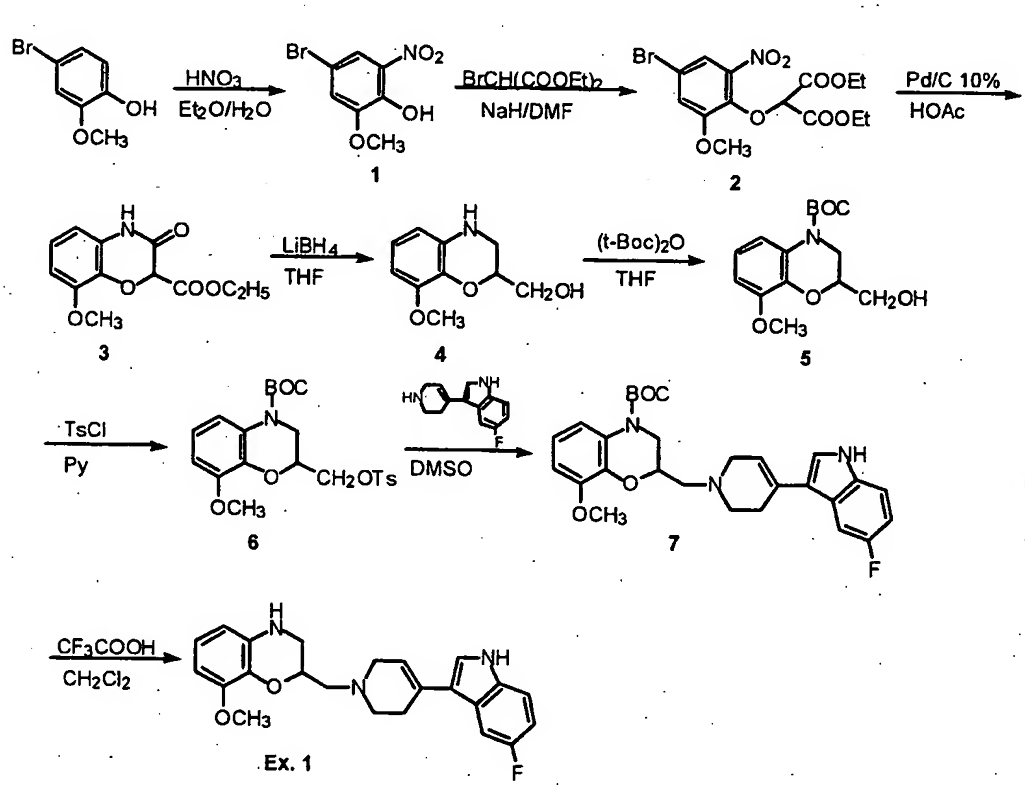
The starting materials/reactants used in the processes above are known or can be made by methods known in the art from readily available materials by processes known or readily apparent to those skilled in the art.

Examples of α-amino protecting groups are well known in the art and may be (1) the acyl type protecting groups illustrated by the following: formyl, trifluoroacetyl, phthalyl, *p*-toluenesulfonyl (tosyl) and *o*-nitrophenylsulfenyl; (2) aromatic urethane type protecting groups illustrated by benzyloxycarbonyl and substituted benzyloxycarbonyl such as *p*-chlorobenzyloxycarbonyl, *p*-nitrobenzylcarbonyl; (3) aliphatic urethane protecting groups illustrated by *tert*-butyloxycarbonyl, diisopropylmethoxycarbonyl, isopropyloxycarbonyl, allyloxycarbonyl, 2,2,2-trichloroethoxycarbonyl, amyloxycarbonyl; (4) cycloalkyl urethane type protecting groups illustrated by cyclopentyloxycarbonyl, adamantyloxycarbonyl,

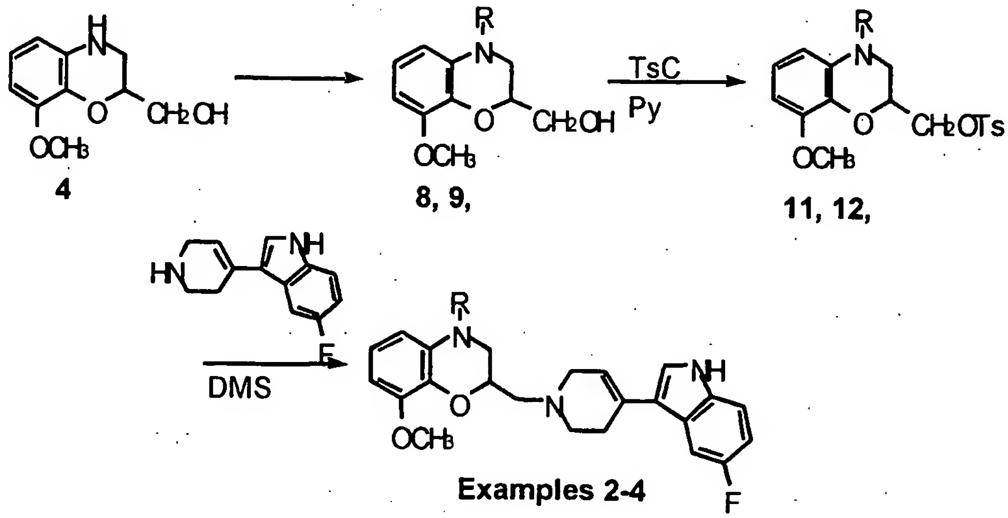
cyclohexyloxycarbonyl; (5) thiourethane type protecting groups such as phenylthiocarbonyl; (6) alkyl type protecting groups illustrated by triphenylmethyl (trityl); and (7) trialkylsilane groups such as trimethylsilane.

The following reaction schemes 1 to 5 illustrate preferred synthetic routes to the compounds of formula I.

Scheme 1

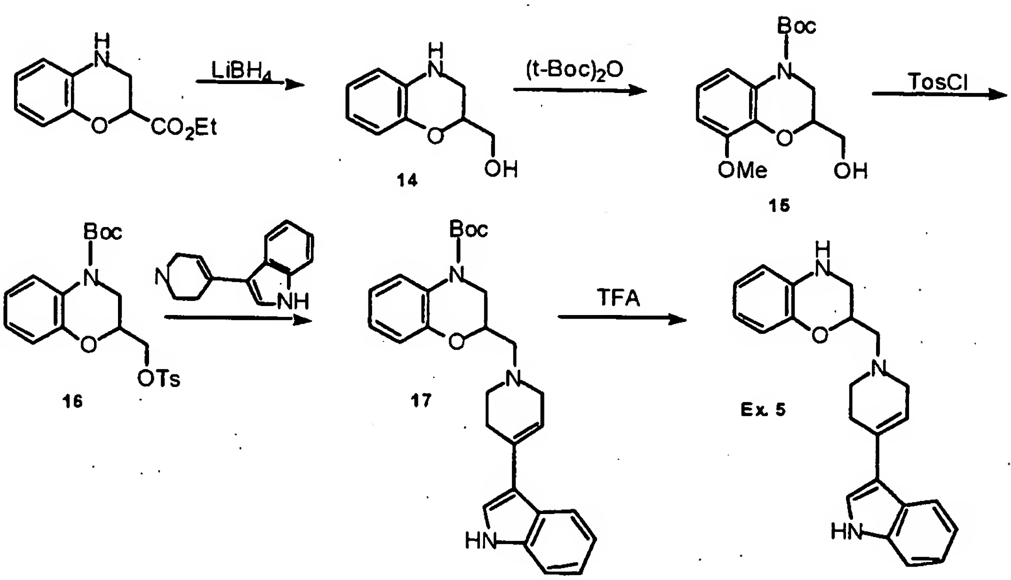


Scheme 2

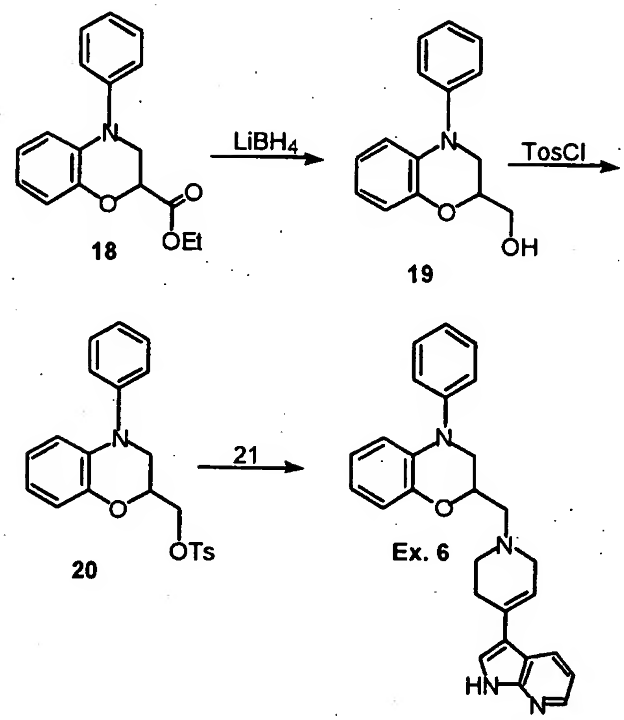


where R is R_3 except hydrogen or a protecting group

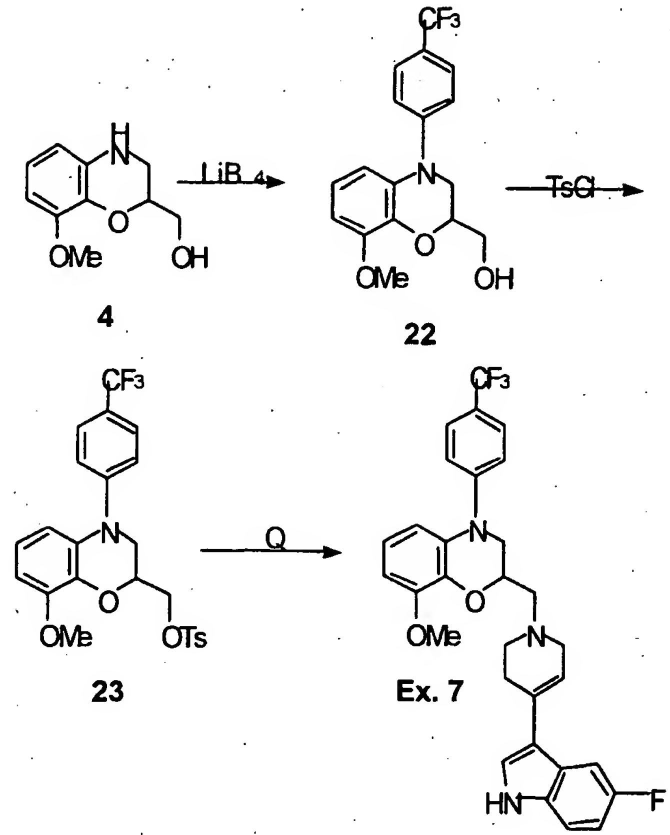
Scheme 3



Scheme 4



Scheme 5



Q = 5-fluoro-3-(1,2,3,6-tetrahydro-4-pyridinyl)-1H-indole

INTERMEDIATE 1

4-Bromo-6-nitroguaicol

To a two-phase, rapidly stirred solution of 4-bromoguaiacol (53.78 g, 0.26 mmol) in ethyl ether (328 ml) and water (109 ml) was added concentrate nitric acid (17 ml) over 25 minutes. The resulting solution was stirred at room temperature for 20 minutes. The ethyl ether was separated and methylene chloride was added to ethyl ether to completely dissolve the yellow crystals. The organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated. Chromatography (1 : 4.5 : 1.5 = ethyl acetate: hexanes: methylene chloride) afforded 32.9 g (50%) of product as a yellow solid: mp 109-110°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ3.95 (3H, s), 7.19 (2H, m), 7.85 (1H, m), 10.7 (1H, s).

Elemental analysis for $C_7H_6BrNO_4$

Calc'd;: C, 33.90; H, 2.44; N, 5.65

Found: C, 33.90; H, 2.32; N, 5.38

INTERMEDIATE 2

2-(4-Bromo-2-methoxy-6-nitro-phenoxy)-malonic acid diethyl ester

A mixture of sodium hydride (0.9 g, 20 mmol) in N,N-dimethylformamide (40 ml) was stirred at room temperature and a solution of nitrophenol (5.0 g, 20 mmol) in N,N-dimethylformamide (10 ml) in was added dropwise and stirred for 45 minutes. The reaction mixture was cooled to 0°C and diethyl bromomalonate (7 ml, 20 mmol) was slowly added to the reaction mixture. The reaction was stirred for 2 hours at ice bath temperature and allowed to warm to room temperature for 48 hours. The mixture was then poured into water and extracted with ethyl acetate, washed with 1N sodium hydroxide, water and brine. The organic layer was dried over anhydrous magnesium sulfate and filtered. The solvent was removed under vacuum. Chromatography (60% ethyl acetate-hexanes) afforded 6.4 g (78.3%) of product as white solid: mp 59-61°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.30 (6H,t, J = 7.04 Hz), 3.88 (3H, s), 4.29 (2H, dq, J = 0.88, 7.04 Hz), 7.20 (1H, d, J = 2.2 Hz), 7.50 (1H, d, J = 2.2Hz).

Elemental analysis for $C_{14}H_{16}BrNO_8$

Calc'd;: C, 41.40; H, 3.97; N, 3.45

Found: C, 41.55; H, 3.76; N, 3.32

INTERMEDIATE 3

8-Methoxy-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazine-2-carboxylic acid ethyl ester

A mixture of Intermediate 2 and 10% palladium on carbon (0.1 g) in acetic acid (10 ml) was hydrogenated at 35 psi for 5 hours. The catalyst was filtered and the solvent removed under vacuum. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with water, brine and dried over anhydrous magnesium sulfate, filtered and the solvent was removed under vacuum to afford a crude solid. Recrystallization in ethyl acetate gave 0.7 g (68%) of product as a white solid: mp 173-174°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ1.25 (3H, t, J

= 7 Hz), 3.92 (3H, s), 4.12-4.30 (m, 2H), 5.27 (1H, s), 6.48 (1H, dd, J = 1.32, 7.92 Hz), 6.66 (1H, dd, J = 1.32, 8.32 Hz), 6.92 (1H, t, J = 8.34 Hz), 8.88 (1H, s); MS (+) ESI *m/e* 252 (M^+).

Elemental analysis for $C_{12}H_{13}NO_5$ •0.25H_2O

Calc'd;:	C, 56.35; H, 5.32; N, 5.47
Found:	C, 56.36; H, 5.02; N, 5.38

INTERMEDIATE 4

(8-Methoxy-3,4-dihydro-2H-benzo[1,4]oxazin-2-yl)-methanol

A mixture of Intermediate 3 (2.3 g, 9.2 mmol) in tetrahydrofuran (200 ml) was stirred at room temperature and lithium borohydride (0.9 g, 42 mmol) was added to above solution in small portions. The reaction mixture was heated to 65°C for 20 hours. The excess lithium borohydride was destroyed by the cautious addition of water. The mixture was concentrated and extracted with ethyl acetate and washed with brine. The organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated to afford 1.7 g (100%) of a crude product as a white solid: mp 108-110°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.00 (1H,m), 3.30 (1H, m), 3.48 (1H, m), 3.58 (1H, m), 3.66 (3H, s), 3.88 (1H, m), 4.87 (1H, t, J = 5.72 Hz), 5.65 (1H, br), 6.19 (2H, m), 6.55 (1H, t, J = 8.12 Hz).

Elemental analysis for $C_{10}H_{13}NO_8$ •0.15C_4H_8O

Calc'd;:	C, 60.95; H, 6.57; N, 6.88
Found:	C, 61.08; H, 6.86; N, 6.71

INTERMEDIATE 5

2-Hydroxymethyl-8-methoxy-2,3-dihydro-benzo[1,4]oxazine-4-carboxylic acid tert-butyl ester

A mixture of Intermediate 4 (2.5 g, 12.8 mmol) and di-t-butyl dicarbonate (9.2 g, 42 mmol) in anhydrous tetrahydrofuran (100 ml) was heated to reflux temperature for 2 hours. The reaction mixture was concentrated and chromatographed (50% ethyl acetate-hexanes) to afford 1.74 g (46 %) of product as white solid: mp 65-68°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.52 (9H, s), 2.28 (1H, br), 3.76-3.93 (7H, m), 4.40 (1H, m), 6.64 (1H, dd, J = 1.32, 8.12 Hz), 6.82 (1H, t, J = 8.36 Hz), 7.26 (1H, br).

Elemental analysis for $C_{15}H_{21}NO_5$

Calc'd;:	C, 61.00; H, 7.17; N, 4.74
Found:	C, 60.65; H, 7.09; N, 4.70

INTERMEDIATE 6

8-Methoxy-2-(toluene-4-sulfonyloxymethyl)-2,3-dihydro-benzo[1,4]oxazine-4-carboxylic acid tert-butyl ester

A mixture of Intermediate 5 (1.6 g) and p-toluenesulfonyl chloride (2.2 g) in dry pyridine (45 ml) was stirred at room temperature for 18 hours. The reaction mixture was diluted with ethyl acetate and sequentially washed with 2N hydrochloric acid, water and brine. The organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated to give 1.7 g of solid which was recrystallized (10% ethyl acetate-hexanes) to afford 1.5 g (60%) of product as a white solid: mp 72-74°; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.53 (9H, s), 2.44 (3H, s), 3.65 (1H, m), 3.83 (3H, s), 3.98 (1H, m), 4.12 (1H, dd, J = 6.8, 10.56 Hz), 4.24 (1H, dd, J = 4.6, 10.56), 4.45 (1H, m), 6.60 (1H, d, J = 1.32 Hz), 6.82 (1H, t, J = 8.36 Hz), 7.32 (2H, m), 7.79 (2H, m).

Elemental analysis for $C_{22}H_{27}NO_7S$

Calc'd :	C, 58.78; H, 6.05; N, 3.12
Found:	C, 58.45; H, 6.03; N, 3.07

INTERMEDIATE 7

2-[4-(5-Fluoro-1H-indol-3-yl)-3,6-dihydro-2H-pyridin-1-ylmethyl]-8-methoxy-3,4-dihydro-2H-benzo[1,4]oxazine-4-carboxylic acid tert-butyl ester

A mixture of Intermediate 6 (1.3 g, 2.9 mmol) and 5-fluoro-3-(1,2,3,6-tetrahydro-4-pyridinyl)-1H-indole (0.9 g, 4.5 mmol) in anhydrous dimethyl sulfoxide (15 ml) was heated to 80°C for 2 hours. The mixture was poured into water (basic solution) and extracted with ethyl acetate and washed with water and brine. The organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated to give 1.0 g of product. Chromatographed (100 % ethyl acetate) afforded 0.8 g (57.2%) of product as a yellow foam.

INTERMEDIATE 8

(8-Methoxy-4-methyl-3,4-dihydro-2H-benzo[1,4]oxazin-2-yl)-methanol

A mixture of Intermediate 4 (1.5 g, 7.7 mmole), anhydrous potassium carbonate (2.2 g.,1.59 mmole) and methyl iodide in N,N-dimethylformamide (60 ml.) were stirred at room temperature for 6 hours. The reaction mixture was poured in water and extracted with ethyl acetate (3 x 100 ml). The combined organic layers were washed with water (100 ml) and with brine (100 ml). The solution was dried over anhydrous magnesium sulfate, filtered and concentrated to give 1.7 g crude product which was chromatographed (ethyl acetate) to give 1.0 g (63.0% yield) of product as a thick oil:

^{1}H NMR (400 MHz, DMSO-d_6): δ 2.79 (3H, s), 3.00 (1H, m), 3.25 (1H, m), 3.48-3.66 (2H, m), 3.68 (3H, s), 4.07 (1H, m), 4.92 (1H, m) 6.36 (2H, dd, J= 1.32, 8.66 Hz), 6.69 (1H, t, J=8.13Hz); MS *m/e* 209 (M+).

Elemental analysis for $C_{11}H_{15}NO_3$

Calc'd: C, 63.14; H, 7.23; N, 6.69

Found: C, 61.02; H, 7.32; N, 6.44

INTERMEDIATE 9

(8-Methoxy-4-ethyl-3,4-dihydro-2H-benzo[1,4]oxazin-2-yl)-methanol

A mixture of Intermediate 4 (1.2 g, 6.1 mmole), N,N-diisopropylethylamine (0.7 g, 6.1 mmole) and iodoethane (1.4 g, 6.1 mmole) was heated at 65° for 24 hours. The reaction mixture was poured into water (100 ml) and extracted with ethyl acetate (3 x 100 ml). The combined organic layers were washed with water (2 x 100 ml), brine (100 ml), dried over anhydrous magnesium sulfate, filtered and concentrated to give 1.3 g crude product. Chromatography (ethyl acetate) gave 0.9 g (69%) of product as a solid: mp 75-77° C; 1H NMR (400 MHz, DMSO-d_6): δ 1.01 (3H, t, J = 7.03Hz), 3.08 (1H, m), 3.00-3.40 (4H, m), 3.48 (1H, m), 3.00-3.40 (4H, m), 3.48 (1H, m), 3.50 (1H, m), 3.63 (4.00 1H, m), 4.90 (1H, broad), 6.35 (1H, dd, J = 1.13, 8.31Hz), 6.37 (1H, dd, J = 1.10, 8.31 Hz), 6.66 (1H, t, J = 8.13Hz); MS *m/e* 378 (M+).

Elemental anakysis for $C_{12}H_{17}NO_3S$

Calc'd:	C, 60.46; H, 6.14; N, 3.71
Found:	C, 60.63; H, 6.06; N, 3.68

INTERMEDIATE 10

(8-Methoxy-4-propyl-3,4-dihydro-2H-benzo[1,4]oxazin-2-yl)-methanol

Intermediate 10 was prepared in same manner as Intermediate 9 to give 1.4 g. pure product (82 %): mp 42-44^0 C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.85 (3H, t J= 7.52 Hz), 1.50 (2H, q, J = 7.52 Hz), 3.05 (2H,m), 3.17 (1H, m), 3.25 (1H, m), 3.49 (1H, m) 3.61 (1H, m), 3.65 (3H, s), 3.95 (1H, m), 4.88 (1H ,broad), 6.25 (1H, d J=8.11 Hz), 6.32 (1H, d, J=7.95 Hz), 6.63 (1H, t J=8.11 Hz) IR (KBr) 3510 cm^{-1}; MS *m/e* 238 (M+).

Elemental analysis for $C_{13} H_{19} N O_3$

Calc'd:	C, 65.80; H, 8.07, N,5.90
Found:	C,66.05, H, 8.34, N,5.90

INTERMEDIATE 11

Toluene-4-sulfonic acid 4-methyl-8-methoxy-3,4-dihydro-2H-benzo[1,4]oxazin-2-ylmethyl ester

A mixture of Intermediate 8 (0.9 g, 0.0043 mole) and p-toluenesulfonyl chloride (1.3 g, 0.0068 mole) in pyridine (30 ml) was stirred at room temperature for eighteen hours. The reaction mixture was diluted with ethyl acetate (200 ml) and washed sequentially with 2N hydrochloric acid (2 x 100 ml), water (2 x 100 ml) and brine (100 ml). The solution was dried over anhydrous magnesium sulfate and concentrated to give 1.4 g of solid which was recrystallized (1:9 ethyl acetate/hexane) to give 1.1 g (73.0%) of product: mp 124-126°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.40 (3H, s), 2.73 (3H, s), 3.00 (1H, m), 3.17 (1H, m), 3.68 (3H, s), 4.13 (1H, m), 4.22 (1H, m), 4.37 (1H, m), 6.35 (2H, dd J = 1.32, 8.35 Hz), 6.68 (1H, t, J = 8.13 Hz), 7.46 (2H, dd, J = 0.72, 8.57 Hz), 7.79 (2H, dd, J = 0.72, 8.35 Hz); MS *m/e* 364 (M+H+)

Elemental analysis for $C_{18}H_{21}NO_{3S}S$

Calc'd:	C, 59.49; H, 5.83; N, 3.85
Found:	C, 58.70; H, 5.77; N, 3.76

INTERMEDIATE 12

Toluene-4-sulfonic acid 4-ethyl-8-methoxy-3,4-dihydro-2H-benzo[1,4]oxazin-2-ylmethyl ester

Intermediate 12 was prepared in the same manner as Intermediate 11 using iodoethane to give 1.0 g of pure product in 62.5 % yield: mp 90-91° C; ^{1}H NMR (400 MHz DMSO-d_6): δ 0.96 (3H, t, J = 7.02 Hz), 2.49 (3H, s), 3.00-3.31 (4H, m), 3.68 (3H, s), 4.10-4.30 (3H, m), 6.29-6.35 (2H, d, J = 9.88 Hz), 6.67 (1H, t, J = 8.35 Hz), 7.46 (2H, d, J = 8.13 Hz), 7.81 (2H, d, J = 8.35 Hz); MS *m/e* 378 (M+).

Elemental analysis for $C_{19}H_{23}NO_3S$

Calc'd:	C, 60.46; H, 6.14; N, 3.71
Found:	C, 60.63; H, 6.06; N, 3.68

INTERMEDIATE 13

Toluene-4-sulfonic acid 4-propyl-8-methoxy-3,4-dihydro-2H-benzo[1,4]oxazin-2-ylmethyl ester

Intermediate 13 was prepared in same manner as Intermediate 11 using iodopropane to give 1.5 g product (71.4 %); mp 94-95° C; ^{1}H NMR (400MHz DMSO-d_6): δ 0.83 (3H, t J=7.37), 1.44 (2H, q J=7.25Hz), 2.40 (3H,s), 3-00-3.22 (6H, m), 3.34 (1H, s broad), 3.67 (3H, s), 4.11 (1H, m), 4.25 (1H, m), 6.28 (1H, dd, J=8.1, 1.21 Hz), 6.33 (1H, dd J=8.35, 1.12Hz), 6.66 (1H, t, J =8.13 Hz), 7.46 (2H, d, J=7.90 Hz), 7.81 (2H, d, J=8.35 Hz); MS *m/e* 392 (M+).

Elemental analysis for $C_{20} H_{25} N O_5 S$

Calc'd:	C, 61.36 H, 6.44 N, 3.58
Found:	C, 61.33 H, 6.41 N, 3.55

INTERMEDIATE 14

3,4-Dihydro-2H-benzo[1,4]oxazin-2-yl)-methanol

To a solution of ethyl 2,3-dihydro-benzo[1,4]oxazine-2-carboxylate ester (11.9 g, 19.0 mmol) in anhydrous tetrahydrofuran (60 mL) was added a 2 M solution of lithium borohydride (15 mL) at room temperature. The reaction was allowed to proceed for 1 hour and was then quenched by the slow addition of methanol. After 2 hours, water was slowly added (100 mL) and the reaction mixture was extracted with

ethyl acetate (4 x 100 mL). The organic layer was separated and dried over anhydrous magnesium sulfate, filtered, and the solvent removed under vacuum. Purification by chromatography (ethyl acetate-hexane-methanol-3:6:1) to afford 1.96 g (62 %) of an oil: MS (EI) *m/e* 165 (M+).

INTERMEDIATE 15

2-Hydroxymethyl-2,3-dihydro-benzo[1,4]oxazine-4-carboxylic acid tert-butyl ester

To a solution of 3,4-dihydro-2H-benzo[1,4]oxazin-2-yl)-methanol (10.7 g, 65.0 mmol) prepared above in anhydrous tetrahydrofuran (200 mL) was slowly added di-tert-butyl dicarbonate (62 g) in tetrahydrofuran (40 mL). The reaction was heated to reflux for 4 hours and allowed to cool to room temperature and then poured into water (100 mL) and extracted with ethyl ether (3 x 100 mL). The organic layer was washed with water (2 x 50 mL) and dried over anhydrous sodium sulfate, filtered, and the solvent removed under vacuum. Chromatography (ethyl acetate-hexanes: 1:2) afforded 12.9 g of white solid (75 %): mp 93.5-94.5 °C; MS (EI) 265 (M+).

Elemental analysis calculated for $C_{14}H_{19}NO_4$

Calc'd:	C, 63.38: H, 7.22: N, 5.28
Found:	C, 63.53: H, 7.32: N, 5.38

INTERMEDIATE 16

t-Butyl-2,3-dihydro-benzo[1,4]oxazine-4-carboxylate-2-methyltosylate

A solution of 2-hydroxymethyl-2,3-dihydro-benzo[1,4]oxazine-4-carboxylic acid tert-butyl ester (2.8 g, 10.6 mmol) and p-toluenesulfonyl chloride (3.4 g,) in anhydrous pyridine (45 mL) was allowed to stir overnight at room temperature. The reaction mixture was quenched with 1 N sodium hydroxide (50 mL) and extracted with methylene chloride (5 x 50 mL). The organic layer was washed with water (3 x 50 mL) and dried over anhydrous sodium sulfate, filtered and the solvent removed under vacuum. Chromatography (ethyl acetate-hexane, 1-3) afforded a thick oil: MS (FAB) *m/e* 419 (M+Na).

Elemental analysis calculated for $C_{21}H_{25}NO_6S$

Calc'd:	C, 60.13: H, 6.01: N, 3.34
Found:	C, 60.13: H, 6.11: N, 3.56

INTERMEDIATE 17

2-[4-(1H-indol-3-yl)-3,6-dihydro-2H-pyridin-1-ylmethyl]-3,4-dihydro-2H-benzo[1,4]oxazine-4-carboxylic acid tert-butyl ester

The title compound was prepared in 29 % yield by reacting Intermediate 16 with 3-(1,2,3,6-tetrahydro-4-pyridinyl-1H-indole according to the same procedure used to prepare Intermediate 7.

INTERMEDIATE 18

Ethyl 4-phenyl-2,3-dihydro-benzo[1,4]oxazine-2-carboxylate ester

A solution of ethyl 2,3-dihydro-benzo[1,4]oxazine-2-carboxylate ester (10g, 48 mmol), 1,4-cyclohexanedione (10.8 g, 97 mmol) and p-toluenesulfonic acid (2 g) in toluene (200 mL) was heated to reflux for 4 hours. The solvent was evaporated and the product was purified by chromatography (ethyl acetate-hexane: 1-3) to afford 7.2 g (53 %) of product as a yellow oil: MS (EI) *m/e* 283 (M^+).

INTERMEDIATE 19

(4-Phenyl-3,4-dihydro-2H-benzo[1,4]oxazin-2-yl)-methanol

To a solution of ethyl 4-phenyl-2,3-dihydro-benzo[1,4]oxazine-2-carboxylate ester (6.9 g, (24 mmol) in anhydrous tetrahydrofuran (80 mL) was added 60 mL of 2 M lithium borohydride in tetrahydrofuran (0.12 mol) at room temperature. The reaction mixture was stirred at room temperture for 4 hours and quenched with methanol. The reaction was poured into water (100 mL) and extracted with ether (3x 80 mL) and the combined organic layers dried over anhydrous sodium sulfate, filtered, and the solvent removed under vacuum. Chromatography (ethyl aceate-hexanes; 1-3) afforded 5.7 g (96 %) of product as a clear oil: MS (EI) *m/e* 213 (M^+).

Elemental analysis calculated for $C_{15}H_{15}NO_2$

Calc'd:	C, 74.67: H, 6.27: N, 5.81
Found:	C, 74.21: H, 6.60: N, 5.56

INTERMEDIATE 20

Toluene sulfonic acid 4-phenyl-3,4-dihydro-2H-benzo[1,4]oxazin-2-yl-methyl ester

(4-Phenyl-3,4-dihydro-2H-benzo[1,4]oxazin-2-yl)-methanol (5.6 g, 23 mmol) was reacted according to the procedure as described above for Intermediate 11 to afford 8.2 g (89 %) of the title compound: mp 83-85 °C.

Elemental analysis calculated for $C_{21}H_{21}NO_4S$

Calc'd:	C, 66.82: H, 5.35: N, 3.80
Found:	C, 66.53: H, 5.39: N, 3.40

INTERMEDIATE 21

3-(1,2,3,6-Tetrahydro-pyridin-4-yl)-1H-pyrrolo[2,3-b]pyridine

7-Azaindole (10 g, 85 mmol), 4-piperidone (34 g,0.22 mol) and potassium hydroxide (16.83 g, 0.3 mol) were heated to reflux in 150 ml methanol overnight. The reaction was cooled, filtered and concentrated to give an orange slurry. The slurry was then extracted with methylene chloride and washed with water. The organic layer was dried over anhydrous magnesium, filtered and concentrated to afford 14.2 g (84%) of product as a solid: mp 195-199 °C.

INTERMEDIATE 22

[8-Methoxy-4-(4-trifluoromethyl-phenyl)—3,4-dihydro-2H-benzo[1,4]oxazin-2-yl]-methanol

Intermediate 4 (0.62 g, 3.2 mmol), 4-iodobenzotrifluoride (2.25 g, 8.32 mmol), powdered anhydrous potassium carbonate (1.76 g, 12.8 mmol), electrolytic copper powder (0.81 g, 12.8 mmol) and 18-crown-6 (0.23 g, 0.64 mmol) were refluxed in o-dichlorobenzene (50 mL) for 4 hours under nitrogen. The inorganic salts were removed by filtration of the hot reaction mixture. The solvent was distilled under reduced pressure and the residue was chromatographed (30 % ethyl acetate-hexanes) to afford 0.43 g (40 %) of product as an oil: ^{1}H NMR (400 mHz, $CDCl_3$) δ 2.10 (2H, bs, OH), 3.69 (1H, m), 3.83 (1H, m), 3.89 (3H, s), 3.91 (2H, m), 4.60 (1H, m), 6.53 (1H, dd, J=8.3, 1.4 Hz), 6.71 (1H, dd, J= 8.3, 1.4 Hz), 6.73 (1H, t, J=8.3 Hz),

7.26 (2H, d, J=8.79 Hz), 7.54 (2H, d, J=8.79 Hz); IR (film) 3080, 2900, 1600, 1475, 1375 cm-1; MS *m/e* 494 ((M+H+).

Elemental analysis calculated for $C_{17}H_{16}FNO_3$

Calc'd:	C, 60.18: H, 4.75: N, 4.13
Found:	C, 60.18: H, 4.61: N, 4.37

INTERMEDIATE 23

Toluene-4-sulfonic acid, [8-Methoxy-4-(4-trifluoromethyl-phenyl)-3,4-dihydro-2H-benzo[1,4]oxazin-2-yl]-methyl ester

Intermediate 23 was prepared from Intermediate 22 in the manner as described for Intermediate 16 to give 0.41 g (92 %) of the title compound as an oil: ^{1}H NMR (400 MHz, CDCl3) δ 2.42 (3H,s), 3.63 (2H, m), 3.82 (2 H, m), 3.88 (3H, s), 4.10 (1H, m), 4.41 (1H, m), 4.50 (1H, m), 6.50 (1H, dd, J=8.1, 1.5 Hz), 6.64 (1H, dd, J=8.1, 1.5 Hz), 6.72 (1H, t, J=8.1 Hz), 7.20 (2H, d, J=8.5Hz), 7.27 (2H, d, J=8.1 Hz), 7.54 (2H, d, J=8.5 Hz), 7.68 (2H, d, J=8.1 Hz); IR (film) 3080, 2900, 1600, 1475, 1325 cm-1; MS *m/e* 494 (M+H+).

Elemental analysis calculated for $C_{24}H_{22}F_3NO_5S{\bullet}0.1\ CH_2Cl_2$

Calc'd:	C, 57.66: H, 4.46: N, 2.79
Found:	C, 57.55: H, 4.30: N, 2.82

EXAMPLE 1

2-[4-(5-Fluoro-1H-indol-3-yl)-3,6-dihydro-2H-pyridin-1-ylmethyl]-8-methoxy-3,4-dihydro-2H-benzo[1,4]oxazine

A mixture of Intermediate 7 (0.8 g, 1.6 mmol) in methylene chloride (15 ml) and trifluoroacetic acid (1.5 ml) was stirred at room temperature for 6 hours. The reaction mixture was poured in 10 % sodium bicarbonate and extracted with ethyl acetate. The combined organic layers were washed with water and brine, then dried over anhydrous magnesium sulfate. Filtration and concentration under vacuum followed by chromatography (5% ammonia in methanol-ethyl acetate) afforded 0.3 g (67%) of product as a yellow solid: mp°C. The oxalate salt was prepared in ethanol: mp 162-166 °C.

Elemental analysis for $C_{23}H_{24}FN_3O_2$•$0.8C_2H_2O_4$

Calc'd:	C, 63.48; H, 5.54; N, 9.03
Found:	C, 63.22; H, 5.70; N, 8.87

EXAMPLE 2

2-[4-(5-Fluoro-1H-indol-3-yl)-3,6-dihydro-2H-pyridin-1-ylmethyl]-8-methoxy-4-methyl-3,4-dihydro-2H-benzo[1,4]oxazine

A mixture of Intermediate 11 (4 g, 0.0011 mole), 5-fluoro-3-(1,2,3,6-tetrahydro-4-pyridinyl-1H-indole (0.7 g 0032 mole) and dimethylsulfoxide (15 ml) was heated to 80° for 2 hours. The reaction mixture was poured into water (100 ml) and extracted with ethyl acetate (3 x 100 ml). The combined organic layers were washed with water (100 ml) and brine (100 ml), dried over anhydrous magnesium sulfate, filtered and concentrated to give 0.35 crude product. Chromatography (3% methanol-ethyl acetate) gave 0.8 g (60 %) of product. The oxalate salt was prepared: mp 218-219 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.73 (2H, s broad), 2.82 (3H, s), 3.;09-3.31 (4H, m), 3.43 (1H, m), 3.73 (3H, s), 3.76-3.81 (2H, m), 4.64 (1H, s broad), 6.09 (1H, s, broad), 6.42 (1H, dd, J = 2.85, -8.12Hz), 6.75 (1H, t, J = 8.13Hz), 6.97 (1H, dt, J = 2.42, 9.00Hz), 7.40 (1H, d, J = 8.79Hz), 7.71 (1H, m), 11.38 (1H, bs); IR (KBr) 3300 cm-1; MS *m/e* 408 (M^+).

Elemental analysis for $C_{24}H_{26}F_3O_2$•$C_2H_2O_4$

Calc'd:	C, 62.;73; H, 5.67; N, 3.85
Found:	C, 62.33; H, 5.77; N, 3.76

EXAMPLE 3

2-[4-(5-Fluoro-1H-indol-3-yl)-3,6-dihydro-2H-pyridin-1-ylmethyl]-8-methoxy-4-ethyl-3,4-dihydro-2H-benzo[1,4]oxazine

The title compounds was prepared by treating Intermediate 12 with 5-fluoro-3-(1,2,3,6-tetrahydro-4-pyridinyl)-1H-indole in the same manner as Example 2 to give 9.35 g of product (63 %) which was converted to oxalate salt: mp 197-199° C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.06 (3H, t, J = 6.81), 2.72 (2H, s broad), 3.10-3.41 (9H, m), 3.74 (3H, s), 4.54 (1H, s broad), 6.11 (1H, s), 6.36 (1H, d, J = 8.35Hz), 6.43

(1H, J = 8.35Hz), 6.74 (1H, s), 7.00 (1H, dt, J = 2.74, 9.00), 7.41 (1H, m), 7.61 (2H, m),11.35 (1H, s broad); IR (KBr) 3400, 3300 cm-1; MS *m/e* 422 (M+).

Elemental analysis for $C_{25}H_{28}FN_3O_2$

Calc'd:	C, 63.36; H, 5.91; N, 8.21
Found:	C, 63.48; H, 5.86; N, 8.32

EXAMPLE 4

2-[4-(5-Fluoro-1H-indol-3-yl)-3,6-dihydro-2H-pyridin-1-ylmethyl]-8-methoxy-4-propyl-3,4-dihydro-2H-benzo[1,4]oxazine

The title compound was prepared by treating Intermediate 13 with 5-fluoro-3-(1,2,3,6-tetrahydro-4-pyridinyl-1H-indole in same manner as Example 2 to give 0.3 g (60 %) of product which was converted to oxalate salt: mp 209-211°C; ^{1}H NMR (400 MHz DMSO-d_6): δ 0.88 (3H, t J=7.25Hz), 1.53 (2H, q, J=7.47), 3.11-3.38 (10 H, m), 3.73 (3H, s) 3.75 (1H,m), 4.52 (1H, m), 6.06 (1H, s), 6.41 (2H, dd J=8.11, 0.6Hz) 6.71 (1H, t), 6.99 (1H dt, J=9.00, 2.42Hz), 7.39 (1H, m), 7.57 (2H, m); IR (KBr) 3300 cm-1; MS *m/e* 436 (M+).

Elemental analysis for $C_{26}H_{30}FN_3O_2$

Calc'd:	C, 63.95 H, 6.13 N,7.99
Found:	C, 64.24 H, 6.19 N, 7.98

EXAMPLE 5

2-[4-(1H-Indol-3-yl)-3,6-dihydro-2H-pyridin-1-ylmethyl]-3,4-dihydro-2H-benzo[1,4]oxazine

The title compound was prepared according to the procedure used for Example 1 using Intermediate 17 (31 %). The oxalate salt was prepared to afford an orange solid: mp 135-140 °C

Elemental analysis for $C_{22}H_{23}N_3O{\bullet}C_2H_2O_4$

Calc'd:	C, 66.15 H, 5.78 N,9.64
Found:	C, 67.21 H, 5.84 N, 9.76

EXAMPLE 6

4-Phenyl-2-[4-(1H-pyrrolo[2,3,b]pyridin-3-yl)-3,6-dihydro-2H-pyridin-1-ylmethyl]-3,4-dihydro-2H-benzo[1,4]oxazine

The title compound was prepared by reacting Intermediates 20 and 21 according to the same procedure used to prepare Intermediate 17 to afford 0.35 g (75 %) of product as a white solid: mp 187-188 C; ^{1}H NMR (400 MHz), DMSO-d_6) δ 2.44 (2H, s), 2.66 (3H, m), 2.75 (1H, m), 3.18 (2H, m), 3.55 (1H, dd, J=7.0, 12.5 Hz), 3.76 (1H, dd, J=2.5, 12.5 Hz), 4.41 (1H, m), 6.10 (1H, s), 6.65 (2H, m), 6.82 (2H, m), 7.03 (2H, m), 7.22 (2H, d, J=7.5 Hz), 7.35 (2H, J=7.5 Hz), 7.46 (1H, d, J=2.4 Hz), 8.18 (2H, m) 11.60 (1H, s): IR (3400, 3080, 2900, 2850, 1700, 1500, 1280, 1250 cm^{-1}; MS *m/e* 423 (M+H+).

EXAMPLE 7

2-[4-(5-Fluoro-1H-Indol-3-yl)-3,6-dihydro-2H-pyridin-1-ylmethyl]-8-methoxy-4-(4-trifluoromethyl-phenyl)-3,4-dihydro-2H-benzo[1,4]oxazine

The title compound was prepared by treating 5-fluoro-3-(1,2,3,6-tetrahydro-4-pyridinyl-1H-indole with Intermediate 23 according to the same procedure used to prepare Intermediate 17 to afford 0.12 g (68 %) of product as a solid: mp 181-182 ^{o}C;: ^{1}H NMR (400 MHz), DMSO-δ6) δ 2.65 (2H, m), 3.18 (3H, m), 3.30 (1H, m), 3.61 (2H, m), 3.75 (1H, m), 3.80 (3H, s), 3.90 (1H, d, J=9 Hz), 4.61 (1H, m), 6.06 (1H, s), 6.63 (1H, d, J=8.1 Hz), 6.69 (1H, d, J=8.1 Hz), 6.76 (1H, t, J=8.1 Hz), 6.96 (1H, dt, J=2.85, 9.0 Hz), 7.36 (1H, m), 7.38 (2H, d, J=8.78 Hz), 7.53 (1H, s), 7.55 (1H, m), 7.65 (2H, d, J=8.78 Hz), 11.35 (1H, bs): IR (KBr) 3450, 3080, 2900, 2600, 1750, 1600, 1475, 1325 cm^{-1}; MS *m/e* 538 (M+H+).

The activity of the present compounds is demonstrated by the following standard pharmacological test procedures.

The PCR cloning of the human 5-HT_{1A} receptor subtype from a human genomic library has been described previously by Chanda et al., Mol. Pharmacol., 43:516 (1993). A stable Chinese hamster ovary cell line expressing the human 5-HT_{1A} receptor subtype (5-HT_{1A}.CHO cells) was employed throughout this study. Cells were maintained in DMEM supplemented with 10% fetal calf serum, non-essential amino acids and penicillin/ streptomycin.

Cells were grown to 95-100% confluency as a monolayer before membranes were harvested for binding studies. Cells were gently scraped from the culture plates, transferred to centrifuge tubes, and washed twice by centrifugation (2000 rpm for 10 min., 4°C) in buffer (50 mM Tris; pH 7.5). The resulting pellets were aliquoted and placed at -80•C. On the day of assay, the cells were thawed on ice, and resuspended in buffer. Studies were conducted using [^{3}H]8-OH-DPAT as the radioligand. The binding assay was performed in 96 well microtiter plates in a final total volume of 250 µL of buffer. Comparison experiments were performed by using 7 concentrations of unlabelled drug and a final ligand concentration of 1.5 nM . Non-specific binding was determined in the presence of 10 µM 5HT. Saturation analysis was conducted by using [^{3}H]8-OH-DPAT at concentrations ranging from 0.3-30 nM. Following a 30 minute incubation at room temperature, the reaction was terminated by the addition of ice cold buffer and rapid filtration using a M-96 Brandel Cell Harvester (Gaithersburg, MD) through a GF/B filter presoaked for 30 minutes in 0.5% polyethyleneimine.

A protocol similar to that used by Cheetham et al., Neuropharmacol. , 32:737 (1993) was used to determine the affinity of compounds for the serotonin transporter. Briefly, frontal cortical membranes prepared from male Sprague-Dawley rats were incubated with ^{3}H-paroxetine (0.1 nM) for 60 min at 25°C. All tubes also contained either vehicle, test compound (one to eight concentrations), or a saturating concentration of fluoxetine (10 µM) to define specific binding. All reactions were terminated by the addition of ice cold Tris buffer followed by rapid filtration using a Tom Tech filtration device to separate bound from free ^{3}H-paroxetine. Bound radioactivity was quantitated using a Wallac 1205 Beta Plate® counter. Nonlinear

regression analysis was used to determine IC_{50} values which were converted to Ki values using the method of Cheng and Prusoff, Biochem. Pharmacol., 22:3099 (1973); Ki = IC50/((Radioligand conc.)/(1 + KD)).

The [^{35}S]-GTPγS binding assay was similar to that used by Lazareno and Birdsall, Br. J. Pharmacol. 109:1120 (1993). Briefly, 5-HT_{1A} cloned receptor membrane fragments (as used for 5-HT_{1A} receptor binding assays) were stored at -70 °C until needed. When needed, membranes were rapidly thawed, centrifuged at 40,000 x g for 10 minutes and resuspended at 4 °C for 10 minutes in assay buffer (25 mM HEPES, 3 mM $MgCl_2$, 100 mM NaCl, 1 mM EDTA, 10 uM GDP, 500 mM DTT, pH 8.0). These membranes were then incubated for 30 min at 30 °C with [^{35}S]GTPgS (1 nM) in the presence of vehicle, test compound (one to eight concentrations), or excess 8-OH-DPAT to define maximum agonist response. All reactions are terminated by the addition of ice cold Tris buffer followed by rapid filtration using a Tom Tech® filtration device to separate bound from free [^{35}S]GTPgS. Agonists produce an increase in the amount of [^{35}S]GTPgS bound whereas antagonists produce no increase in binding. Bound radioactivity was counted and analyzed as above.

The following assays were performed by incubating the cells with DMEM containing 25 mM HEPES, 5 mM theophylline and 10 μM pargyline for a period of 20 minutes at 37°C. Functional activity was assessed by treating the cells with forskolin (1 uM final concentration) followed immediately by test compound (6 concentrations) for an additional 10 min at 37°C. In separate experiments, 6 concentrations of antagonist were preincubated for 20 min prior to the addition of 10 nM 8-OH-DPAT and forskolin. The reaction was terminated by removal of the media and addition of 0.5 ml ice cold assay buffer. Plates were stored at -20°C prior to assessment of cAMP formation by a cAMP SPA assay (Amersham).

Example	$5\text{-}HT_{1A}$ (Ki, nM, % Inh.@ .1 μM)	ST (K_i, nM)	GTPγS Emax (%)
1	155	3.7	10
2	140	8.5	97
3	137	12.0	62
4	363	20.0	100
5	805	0.74	57
6	20 %	106	0
7	0 %	505	-

Such compounds are therefore potentially useful for the treatment of depression as well as other serotonin disorders.

The compounds of the present invention may be administered orally or parentally, neat or in combination with conventional pharmaceutical carriers. Applicable solid carriers for pharmaceutical compositions containing the compounds of this invention can include one or more substances which may also act as flavoring agents, lubricants, solubilizers, suspending agents, fillers, glidants, compression aids, binders or tablet-disintegrating agents or an encapsulating material. In powders, the carrier is a finely divided solid which is in admixture with the finely divided active ingredient. In tablets, the active ingredient is mixed with a carrier having the necessary compression properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain up to 99% of the active ingredient. Suitable solid carriers include, for example, calcium phosphate, magnesium stearate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose, methyl cellulose, sodium carboxymethyl cellulose, polyvinylpyrrolidine, low melting waxes and ion exchange resins.

Liquid carriers may be used in preparing solutions, suspensions, emulsions, syrups and elixirs. The active ingredient of this invention can be dissolved or suspended in a pharmaceutically acceptable liquid carrier such as water, an organic

solvent, a mixture of both or pharmaceutically acceptable oils or fat. The liquid carrier can contain other suitable pharmaceutical additives such as solubilizers, emulsifiers, buffers, preservatives, sweeteners, flavoring agents, suspending agents, thickening agents, colors, viscosity regulators, stabilizers or osmo-regulators. Suitable examples of liquid carriers for oral and parenteral administration include water (particularly containing additives as above e.g. cellulose derivatives, preferably sodium carboxymethyl cellulose solution), alcohols (including monohydric alcohols and polyhydric alcohols e.g. glycols) and their derivatives, and oils (e.g. fractionated coconut oil and arachis oil). For parenteral administration the carrier can also be an oily ester such as ethyl oleate and isopropyl myristate. Sterile liquid carriers are used in sterile liquid form compositions for parenteral administration.

Liquid pharmaceutical compositions which are sterile solutions or suspensions can be utilized by, for example, intramuscular, intraperitoneal or subcutaneous injection. Sterile solutions can also be administered intravenously. Oral administration may be either liquid or solid composition form.

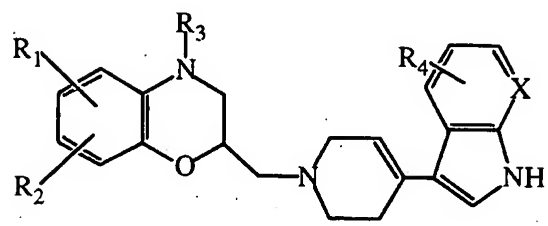
Preferably the pharmaceutical composition is in unit dosage form, e.g. as tablets or capsules. In such form, the composition is sub-divided in unit dose containing appropriate quantities of the active ingredient; the unit dosage forms can be packaged compositions, for example packeted powders, vials, ampoules, prefilled syringes or sachets containing liquids. The unit dosage form can be, for example, a capsule or tablet itself, or it can be the appropriate number of any such compositions in package form.

The dosage to be used in the treatment of a specific psychosis must be subjectively determined by the attending physician. The variables involved include the specific psychosis and the size, age and response pattern of the patient.

The present invention may be embodied in other specific forms without departing from the spirit and essential attributes thereof and accordingly, reference should be made to the appended claims, rather than to the foregoing specification, as indicating the scope of the invention.

WHAT IS CLAIMED IS:

1. A compound of the formula:



(I)

wherein:

R_1 is hydrogen or halogen;

R_2 is hydrogen, alkoxy or carboximide;

R_3 is hydrogen, alkyl, alkylaryl, aryl or substituted aryl;

R_4 is hydrogen, CN, halogen or carboximide; and

X is CH or N; or

pharmaceutically acceptable salts thereof.

2. A compound as claimed in claim 1 where R_1 is hydrogen.

3. A compound as claimed in claim 1 or 2 where R_2 is alkoxy or hydrogen.

4. A compound as claimed in any of claims 1 to 3 where R_3 is hydrogen, alkyl or arylalkyl.

5. A compound as claimed in any of claims 1 to 4 where R_4 is halogen or hydrogen.

6. A compound as claimed in any of claims 1 to 5, wherein:

R_1 is hydrogen;

R_2 is alkoxy or hydrogen;

R_3 is hydrogen, alkyl or alkylaryl;
R_4 is halogen or hydrogen; and
X is CH or N; or
pharmaceutically acceptable salt thereof.

7. The compound of claim 1 which is 2-[4-(5-fluoro-1H-indol-3-yl)-3,6-dihydro-2H-pyridin-1-ylmethyl]-8-methoxy-3,4-dihydro-2H-benzo[1,4]oxazine or pharmaceutically acceptable salt thereof.

8. The compound of claim 1 which is 2-[4-(5-fluoro-1H-indol-3-yl)-3,6-dihydro-2H-pyridin-1-ylmethyl]-8-methoxy-4-methyl-3,4-dihydro-2H-benzo[1,4]oxazine or pharmaceutically acceptable salt thereof.

9. The compound of claim 1 which is 2-[4-(5-fluoro-1H-indol-3-yl)-3,6-dihydro-2H-pyridin-1-ylmethyl)-8-methoxy-4-ethyl-3,4-dihydro-2H-benzo[1,4]oxazine or pharmaceutically acceptable salt thereof.

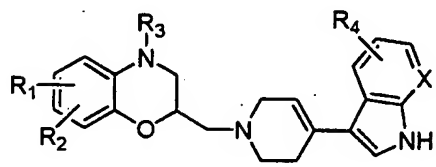
10. The compound of claim 1 which is 2-[4-(5-fluoro-1H-indol-3-yl)-3,6-dihydro-2H-pyridin-1-ylmethyl]-8-methoxy-4-propyl-3,4-dihydro-2H-benzo[1,4]oxazine or pharmaceutically acceptable salt thereof.

11. The compound of claim 1 which is 2-[4-(1H-indol-3-yl)-3,6-dihydro-2H-pyridin-1-ylmethyl]-3,4-dihydro-2H-benzo[1,4]oxazine or pharmaceutically acceptable salt thereof.

12. The compound of claim 1 which is 4-phenyl-2-[4-(1H-pyrrolo[2,3,6]pyridin-3-yl)-3,6-dihydro-2H-pyridin-1-ylmethyl]-3,4-dihydro-2H-benzo[1,4]oxazine or pharmaceutically acceptable salt thereof.

13. The compound of claim 1 which is 2-[4-(5-fluoro-1H-indol-3-yl)-3,6-dihydro-2H-pyridin-1-ylmethyl]-8-methoxy-4-(4-trifluoromethyl-phenyl)-3,4-dihydro-2H-benzo[1,4]oxazine or pharmaceutically acceptable salt thereof..

14. A process for preparing a compound of formula I



wherein:

R_1 is hydrogen or halogen;

R_2 is hydrogen, alkoxy or carboximide;

R_3 is hydrogen, alkyl, arylalkyl, aryl or substituted aryl;

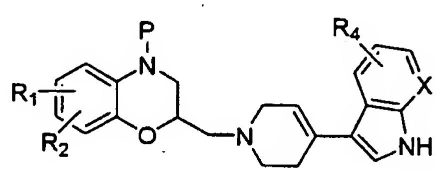
R_4 is hydrogen, CN, halogen or carboximide; and

X is CH or N; or

a pharmaceutically acceptable salt thereof,

which comprises one of the following;

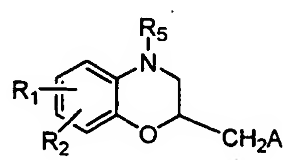
a) deprotecting a compound of formula II



(II)

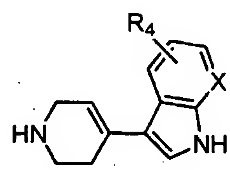
wherein R_1, R_2, R_4 and X are as defined in claim 1 and P is an amino protecting group to give a compound of formula I wherein R_3 is hydrogen; or

b) reacting a compound of formula III



(III)

wherein R_1 and R_2 are as defined in claim 1, A is a leaving group, and R_5 is alkyl, arylalkyl, aryl, substituted aryl or an amino protecting group P, with a compound of formula IV



(IV)

wherein R_4 and X are as defined above, and if required removing a protecting group P if present, to give a compound of formula I; or

c) acidifying a basic compound of formula I with a pharmaceutically acceptable acid to give a pharmaceutically acceptable salt;

or

d) resolving a mixture (e.g racemate) of optically active isomers of a compound of formula I to isolate one enantiomer or diastereomer substantially free of the other enantiomer or diastereomers.

15. A process for preparing a compound as claimed in claim 14 wherein P is a BOC protecting group.

16. A pharmaceutical composition comprising a compound of the formula (I) as claimed in claim 1 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

17. A method for treating depression in a patient in need thereof, comprising administering to said patient an antidepressant effective amount of a compound of the formula (I) as claimed in claim 1 or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 00/00347

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D413/14 C07D471/04 A61K31/538 A61P25/24
//(C07D471/04,221:00,209:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 89 07596 A (ERBA CARLO SPA) 24 August 1989 (1989-08-24) cited in the application claims	1-17
A	A.-S. BOURLOT ET AL.: "New substituted 1,4-benzoxazine derivatives with potential intracellular calcium activity" JOURNAL OF MEDICINAL CHEMISTRY., vol. 41, no. 17, 1998, pages 3142-3158, XP002136635 AMERICAN CHEMICAL SOCIETY. WASHINGTON., US ISSN: 0022-2623 the whole document	1-17
P,A	WO 99 51592 A (AMERICAN HOME PROD) 14 October 1999 (1999-10-14) claims	1-17

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
2 May 2000	17/05/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Chouly, J

Form PCT/ISA/210 (second sheet) (July 1992)

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 17
   because they relate to subject matter not required to be searched by this Authority, namely:
   Remark: Although claim 17 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
   because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
   because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 00/00347

Patent document cited in search report		Publication date	Patent family member(s)			Publication date
WO 8907596	A	24-08-1989	AT	96788	T	15-11-1993
			AU	3063489	A	06-09-1989
			CA	1327575	A	08-03-1994
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			DE	68910451	T	03-03-1994
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			IL	89035	A	30-05-1994
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			US	5084454	A	28-01-1992
			US	5229383	A	20-07-1993
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WO 9951592	A	14-10-1999	AU	3476599	A	25-10-1999